PROFESSOR WERNER Z´GRAGGEN (Orcid ID : 0000-0002-5684-4419)

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Editorial: Critical Illness Myopathy: Glucocorticoids revisited?

Werner J. Z'Graggen[1] and Joerg C. Schefold[2]

[1] Departments of Neurosurgery and Neurology, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland

[2] Department of Intensive Care Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Correspondence to:

W.J. Z'Graggen

Departments of Neurosurgery and Neurology, University Hospital Bern, Freiburgstrasse 10, 3010 Bern, Switzerland

E-mail: werner.zgraggen@insel.ch

Tel: +41 31 632 21 11

Fax: +41 31 632 30 11

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Over the past decades, survival rates of critical illness have constantly increased. As a consequence, the incidences of important complications of intensive care unit (ICU) treatment become more and more prevalent. Critical illness myopathy (CIM) belongs to one of the most frequent neuromuscular complications and its presence is associated with prolonged need for mechanical ventilation and ICU stay, increased morbidity and mortality 1,2. High-dose glucocorticoid (GC) treatment was early after the initial description of CIM postulated to be a major triggering factor for the development of the disease. In the current issue of Acta Physiologica, Akkad et al. investigate the effects of two GC drugs (prednisolone and a new dissociative GC termed vamorolone) on CIM development3. They use a well-established animal model for CIM, which mimics ICU conditions by combining three important risk factors for CIM: sedation, pharmacological immobilization, and mechanical ventilation. Whereas animals not exposed to GCs developed a typical CIM geno- and phenotype, prednisolone and vamorolone treatment resulted both in improved survival rates, reduced body weight loss, decreased weakness, and milder CIM- associated muscular structural changes. Further, Vamorolone treatment was superior to prednisolone in improving CIM outcome and, importantly, did not induce atrophy and dysfunction of fast-twitch muscle fibers, as observed following treatment with prednisolone.

The study of Akkad et al. addresses a very important topic of modern ICU treatment. In fact, GC treatment was widely studied in different ICU conditions including septic shock and acute respiratory distress syndrome (ARDS). Today, low-dose GC treatment is an important treatment option, in patients with catecholamine-"refractory" hemodynamic shock or in patients with ARDS, resulting in faster shock resolution and/or shorter time on mechanical ventilation. However, more "liberal" use of GC treatment in critical illness was always a matter of controversy. One major argument against a more "liberal" GC use on the ICU embraced concerns about their potential role as a triggering factor for the development of CIM. In fact, the hypothesis that CIM is linked to GC treatment was raised in parallel to the first reports of this disease. These reports emerged in patients treated with high doses of GCs and/or neuromuscular blocking agents. Meanwhile, several clinical studies aimed to link CIM or the so-called ICU-acquired weakness (ICUAW) with GC treatment and reported contradictory results.

However, one possible factor that affected the outcome of these studies was the selected primary endpoint. While *definite diagnosis of CIM* is based on multimodal diagnostic criteria consisting of typical patient history, clinical examination, electrophysiological studies and, ultimately, a muscle biopsy that shows primary myopathy with myosin loss, the diagnostic criteria of ICUAW only rely on patient history and clinical examination[4]. Additional electrophysiology is not mandatory. However, if additional electrophysiology is performed and findings are typical, diagnosis of *probable CIM* can be made according to the published diagnostic criteria[4]. In this context, it should be remembered that the clinical picture of weakness may also be caused by critical illness polyneuropathy (CIP), another ICU treatment related complication. CIP often co-exists with CIM as critical illness polyneuromyopathy. In daily practice, differential diagnosis can sometimes be difficult and may need extensive electrophysiological investigation[4]. Importantly, the term ICUAW does not discriminate between CIM and CIP. Most studies investigating an association of GC treatment and occurrence of muscle weakness during ICU stay used the primary endpoint ICUAW and refrained from an invasive diagnosis via muscular biopsy. Interestingly, a recently published meta-analysis on GC use and ICUAW based on one randomized controlled trial and 17 prospective cohort studies, found a significant association of GC treatment and ICUAW (OR 1.84, 95% CI 1.26-2.67)[5]. However, subgroup analyses revealed that the association of GC treatment with ICUAW is only found in studies that used a purely clinical definition for ICUAW (OR 2.06, 95% CI 1.27-3.33). When additional neurophysiological criteria are applied, this association was not observed anymore (OR 1.65, 95% CI 0.92-2.95). Hence, in patients with probable CIM, GC treatment is mostly likely not an additional causative factor.

Undoubtedly, GC treatment is associated with muscular side effects such as atrophy of skeletal muscles, loss of thick filaments, acceleration of protein degradation, and increased expression of corticosteroid receptors. Respective effects seem dose- and time- dependent. Vamorolone, is a member of a new class of synthetic glucocorticoids that are collectively referred as “dissociative GCs”. The hallmarks of vamorolone are its potent inhibition of pro-inflammatory pathways via GC-receptor binding, antagonism for the mineralocorticoid receptor, and membrane-stabilizing effects

with reduced negative side effects compared to traditional GCs. The drug was already successfully tested in a phase I trial and very recently in a Phase IIa trial in 48 patients with Duchenne muscular dystrophy [6,7]. Respective trial data show a superior safety profile of vamorolone when compared to prednisone, a potent anti-inflammatory action and potential antagonistic effects on the mineralocorticoid receptor. Although further trials are required to confirm these first very encouraging results, vamorolone seems to have the potential to change GC therapy in general. The current elegant study by Akkad et al. not only confirms the safety profile of the drug but also shows the potential of vamorolone to reduce the risk of negative muscular outcomes as a complication of ICU treatment. The latter may reduce sequels of CIM such as prolonged duration of ICU- and hospital stay, need for rehabilitation, and delayed return to work or even permanent inability to work.

Conflict of interest: None

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